REMARKS

Reconsideration of the present application is respectfully requested in view of the Amendments submitted herewith and the following remarks. As an initial matter, Applicants thank the Examiner for her time to discuss the present application during a teleconference with the undersigned representative on March 30, 2009. Claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 were pending. Applicants hereby cancel claims 14, 21, and 23 without acquiescence to any rejection and without prejudice to prosecuting the cancelled subject matter in a related divisional, continuation, or continuation-in-part application. Claims 2, 5, and 11 have been amended to incorporate the feature previously recited in claim 14, which had depended from claims 2, 5, and 11. Applicants have amended claims 2-5, 7, 11, 12, 17-20, 27, and 34-39 and added new claims 40-45 to point out with greater particularity and to claim distinctly certain embodiments of Applicants' invention. In view of the amendments to claim 34, new claims 40-42 have been added and properly refer to terms in the claims from which claims 40-42 respectively depend. No new matter has been added to the application by these amendments. Support for the amended claims may be found throughout the specification, for example, at page 19, lines 24-27; page 25, lines 12-15; page 57, line 21 through page 62, line 13 (Examples 9 and 10); and at page 62, line 15 through page 66, line 15 (Example 11). Upon entry of the amendments submitted herewith, claims 2-5, 7, 11, 12, 17-20, 24-27, and 34-45 will be under examination.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejected claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 under 35 U.S.C. § 112, first paragraph, asserting that the scope of the claims is not commensurate with the disclosure of the specification.

Applicants respectfully traverse this rejection and submit that as disclosed in the specification and recited in the instant claims, Applicants fully enabled the claimed subject matter at the time the application was filed. Applicants submit that in view of the abundant guidance and direction provided in the specification (including working examples), the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables

a skilled artisan to make and use the claimed compositions comprising a Neisserial surface protein A (NspA) polypeptide, or variants and fragments thereof, and related methods, readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The claims as amended herewith are directed, in pertinent part, to immunogenic compositions comprising a liposome formulated with (a) at least one polypeptide that comprises an amino acid sequence at least 90% identical to the amino acid sequence set forth in SEQ ID NO:2; (b) a polypeptide that comprises an immunogenic fragment comprising at least 10 contiguous amino acids of SEQ ID NO:2; or (c) a chimeric polypeptide comprising two or more immunogenic fragments that comprise at least contiguous 10 amino acids of SEQ ID NO:2, wherein the liposome comprises a bacterial phospholipid that is selected from *E. coli*, *N. meningitidis*, and *N. lactamica*, and to related compositions and methods of using the claimed compositions. The polypeptides, as recited in the claims, are capable of eliciting antibodies that specifically bind to a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 (*see also, e.g.,* specification at page 12, lines 16-20).

Applicants respectfully disagree with the assertion by the Examiner that "the specification gives no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced" (*see* Action at page 3, second sentence of full paragraph). As previously made of record (*see* Reply and Amendment submitted to the U.S. Patent and Trademark Office (PTO) with a Request for Continued Examination on August 6, 2008 in response to an Office Action dated August 7, 2007; *see* Reply and Amendment submitted September 11, 2006 in response to an Office Action dated March 10, 2006), the specification describes extensive mutation, modeling, and immunological studies that teach a person skilled in the art which regions of NspA are likely to be immunogenic and which regions are expected to be less immunogenic. The specification thus provides sufficient guidance, including working examples, that teach a person skilled in the art which particular regions of the NspA polypeptide may be amenable to a substitution, deletion, or addition of an amino acid.

The specification teaches which regions comprise immunogenic epitopes, thereby teaching regions of NspA from which immunogenic fragments may be derived and teaching which regions of the polypeptide may be less amendable to modification. The specification

teaches which regions are exposed on the exterior (*e.g.,* L1-L4) of the cell surface of *N. meningitidis* cells (*see* page 36, lines 15 through page 37, line 2). Site directed mutations introduced into the amino acid sequences of each of the four surface exposed loops (*i.e.,* L1-L4), showed that L3 (amino acids at positions 108-125 of SEQ ID NO:2) or L3 + L2 (amino acids 68-80 of SEQ ID NO:2) contained epitopes to which bactericidal antibodies bound (referred to therein as Group 1 antibodies; *see, e.g.,* page 41, lines 18-21; page 48, line 5 through page 52, line 11; Table 7 (Example 5)). Therefore, as taught in the specification and recited in the present claims, immunogenic regions of the Neisseria polypeptide include contiguous amino acids at positions 68-80 and 108-125 of SEQ ID NO:2.

The specification also teaches which amino acids within NspA may be more amenable to modification. The specification teaches which regions are included in transmembrane regions (*e.g.,* M1-M8) and which regions are exposed on the periplasmic side (*e.g.,* T1-T3). These regions are less likely to comprise immunogenic epitopes. By way of example, the specification describes in working examples that two peptides, between residues 41-55 and between residues 141-150 of SEQ ID NO:2, bind specifically to an antibody that does not bind to the surface of intact meningococcal cells. These two peptide regions are embedded in the meningococcal outer membrane and are thus not accessible to a bactericidal antibody (*see, e.g.,* page 48, lines 15-26).

Applicants disagree with the assertions by the Examiner (*see* Action, page 4) that multiple mutations *may* result in loss of the ability of polyclonal sera to bind to a polypeptide, and that this hypothetical renders the present claims not enabled by the specification. Applicants submit, as previously made of record, that the law is well settled that to satisfy the enablement requirement, an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polypeptide variants may be made, Applicants are not required to list all operable embodiments

of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984). Also contrary to the assertions in the Action (*see* page 4, middle of page), not only does the specification describe in detail immunogenic regions of the polypeptide, the specification does indeed provide guidance with respect to the effects of different amino acid substitutions on the function of the NspA polypeptide. Certain mutations within the L3 loop resulted in loss of the capability of particular anti-NspA monoclonal antibodies to bind to the polypeptide (*see e.g.,* page 51, lines 1-6, Table 7, Nm3 mutant).

The assertions in the Office Action that a single amino acid substitution may alter the function of a polypeptide (*see* Action, page 4, citing Mikayama) and that the significance of particular amino acids in a polypeptide "must be determined from case to case by painstaking experimental study" (*see* Action, page 5, citing Rudinger) fail to appreciate and acknowledge the state of the art and the level of skill of a person skilled in the art at the time of filing the present application. As previously made of record, even though according to Rudinger, "painstaking experimental study" may have been required in 1976 to make variants and immunogenic fragments of a polypeptide, given the extensive disclosure in the present application and given the knowledge in the art *approximately 25 years later at the time of filing the instant application*, such experimentation is routine.

Because only a single amino acid change in the GIF polypeptide discussed in Mikayama is attributable to a change in function, the results in Mikayama suggest that if a person skilled in the art were to make polypeptide variants using the human GIF polypeptide sequence described therein as a starting point, the skilled person would identify variants that were highly structurally related and that exhibited the same function with far greater probability than variants that did not exhibit the same function. As suggested by the results in Mikayama, the ability of a person skilled in the polypeptide art to identify a polypeptide that has lost a claimed function or property is far more unpredictable than making a polypeptide variant that has the claimed structural features and that exhibits a claimed correlative function.

Moreover, with respect to the immunological art, according to textbook knowledge, "the number of different antibodies which may be produced to an antigen is *high*"

and "[d]ifferent antibodies to an antigen often bind to epitopes which overlap on the antigen surface" (emphasis added) (Roitt et al. (*Immunology*, 1998, 4th Edition, Mosby, London, page 7.7); reference AG submitted with Information Disclosure Statement on August 6, 2008). Persons skilled in the immunology and vaccine arts readily appreciate that an advantage of using a polypeptide as an immunogen when the polypeptide immunogen induces a polyclonal immune response is that most mutations introduced into the polypeptide when expressed by an infectious disease organism will not destroy all the immunoepitopes that are recognized by antibodies induced by the polypeptide immunogen. Lipman et al. teach that "because [polyclonal antibodies] are heterogeneous and recognize a host of antigenic epitopes, the effect of change on a single or small number of epitopes is less likely to be significant" (Lipman et al., *ILAR Journal*, 46: 258-268, 261, Col. 1 (2005) reference AF, submitted with Information Disclosure Statement on August 6, 2008). Indeed, these properties associated with a polyclonal response to an antigen motivate persons skilled in the immunology art to develop vaccines for effectively immunizing individuals against various communicable pathogens.

As noted above, the present claims are directed to immunogenic compositions comprising a liposome, as recited, and at least one polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO:2; comprising an immunogenic fragment, as recited; or comprising a chimeric polypeptide, as recited; and to methods for inducing an immune response against *N. meningitidis*, wherein the immune response comprising eliciting antibodies that specifically bind to a polypeptide consisting of the amino acid sequence of SEQ ID NO:2. The present application describes that compositions comprising an exemplary NspA polypeptide formulated with differing liposome induced high antibody titers in immunized mice and rabbits (*see, e.g.,* page 60, line 7 through page 62, line 13 (Example 10). Moreover, rabbit antisera from the immunized animals comprised antibodies that had bactericidal activity against multiple strains of *N. meningitidis* (*see, e.g.,* page 62, line 16 through page 66, line 15 (Example 11). Without citation to any reference in the bacterial vaccine art, the Examiner asserts that "challenge experiments are needed to demonstrate success [in the bacterial vaccine art]" (see Action page 7) and asserts that "three major considerations" determine the effectiveness of an antigen as a vaccine candidate. Contrary to this assertion, persons skilled in the *N. meningitidis*

art have recognized that the capability of a *N. meningitidis* antigen to induce antibodies that have bactericidal activity is predictive of the capability of the antigen to induce an effective immune response (*see, e.g.,* Jodar et al., *Lancet* 359:1499-508 (2002), evaluating vaccines that in mice, "elicit serum bactericidal antibodies, which are the serological hallmark of protective immunity in man"; see Abstract; enclosed for the Examiner's convenience).

Applicants respectfully point out that in response to a prior Office Action (*see* Reply and Amendment submitted August 6, 2008 in response to an Office Action dated August 7, 2007), Applicants made of record that in the present application and in the art the NspA polypeptide is described as a conserved cell-surface polypeptide expressed by numerous strains of *Neisseria meningitidis*, which represent divergent serogroups A, B, and C (*see, e.g.,* specification at page 4, lines 15-20, and references cited therein; U.S. Patent No. 6,287,574, demonstrating that the NspA antigen is present on more than seventy different *Neisseria meningitidis* bacterial isolates). Indeed, NspA polypeptides that share at least 90% identity with the amino acid sequence in SEQ ID NO:2 have been identified (*see, e.g.,* U.S. Patent No. 6,287,574). If a person skilled in the art desired to clone and sequence the NspA polypeptide from any *N. meningitidis* strain, the skilled person may do so using any one of several known methods practiced in the art. Furthermore, because the exemplary NspA polypeptide described in the present application induced an immune response comprising antibodies that exhibited bactericidal activity against different strains of *N. meningitidis* (*see* page 66 (Table 11); *see also* U.S. Patent No. 6,287,574), a person skilled in the art would predict that an Nspa polypeptide isolated from any one of these strains would induce a similar response, even though the amino acid sequence would, more likely than not, not be identical to the amino acid sequence of SEQ ID NO:2.

Contrary to the assertion by the Examiner, citing *Genentech Inc. v. Novo Nordisk A/S* (Fed. Cir. 1996), Applicants have provided far more than "vague intimations of general ideas that may or may not be workable," by providing extensive disclosure in the application, including working examples, demonstrating the utility of the claimed compositions as well as providing abundant guidance to teach a person skilled in the art how to make and use the claimed embodiments. Applicants submit that the scope of the present claims is commensurate with the

disclosure in the specification, especially when the extensive guidance in the specification, the state of the art, and the level of a person skilled in the art are properly considered. The Examiner asserts that "three major considerations must be raised" when "considering a bacterial antigen as a vaccine candidate," (as noted above, no citation to any related art is provided), and then further asserts that "even when an antigen meets these three considerations, further testing often indicates that the antigen will not be effective as a vaccine" (*see* Action, page 8, first full paragraph). The Federal Circuit noted in *In re Brana* (51 F.3d 1560 (Fed. Cir. 1995) that usefulness in the context of pharmaceutical inventions includes the expectation of further research and development, and that efficacy in humans is not necessary for finding a compound useful and enabled under 35 U.S.C. § 112, first paragraph. The court also stated, "[t]he stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Citing *In re Krimmel* (130 U.S.P.Q. 205 (C.C.P.A. 1961)), the court noted as well that this principle applies "even though it may eventually appear that the compound is without value in the treatment of humans." *Id.*

As discussed above, applicants need not describe each and every embodiment encompassed by the claims when an application teaches a person skilled in the art how to make and use the claimed embodiments without undue experimentation. The Examiner is essentially setting forth an *a priori* predictability requirement; however *a priori* predictability is <u>not</u> an enablement requirement. The courts have rejected a "reasonable certainty" standard for enablement disclosure, which is an even less rigorous standard than *a priori* predictability (*see, e.g., In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976) (opining that if *Rainer*, as improperly relied on by the dissent, "stands for the proposition that the disclosure must provide guidance which will enable one skilled in the art to determine, w*ith reasonable certainty before performing the reaction*, whether the claimed product will be obtained…then *all* 'experimentation' is 'undue,' since the term 'experimentation' implies that the success of the particular activity is *uncertain*") (emphasis added)).

The majority in *Angstadt* states that a "reasonable certainty" standard goes against the basic policy of the Patent Act, which is to encourage disclosure (*see In re Angstadt* at 503). The court states that "[d]epriving inventors of claims which adequately protect them and limiting

them to claims *which practically invite appropriation of the invention* while avoiding infringement inevitably has the effect of suppressing disclosure." See *Id.* at 504 (emphasis added).

In the present application, Applicants have provided abundant guidance, including working examples, that teach a person skilled in the art how to make and use the claimed compositions comprising bacterial phospholipid liposomes and NspA polypeptides and to make and use compositions comprising these polypeptides, readily and without undue experimentation. Given the skill level of a person skilled in the art, the state of the art, and the present disclosure, if the claimed subject matter is limited to use of the NspA polypeptide having only a single, disclosed sequence, a person skilled in the art can, readily and with *trivial* effort, *appropriate* polypeptides that are outside the scope of the claim by using routine, commonly practiced techniques. Such limited scope is not commensurate with Applicants' significant contribution to the medical art, describing compositions that may be useful for treating and preventing *N. meningitidis* infections.

Accordingly, Applicants submit that the scope of the present claims is commensurate with the disclosure in the specification, satisfying the requirements for enablement under 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejected claims 2-4, 7, 12, 14, 17-21, 23-27, and 34-35 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification.

Applicants respectfully traverse this rejection and submit that, as disclosed in the specification and recited in the instant claims, the application reasonably conveys to a person skilled in the art that Applicants possessed the claimed invention at the time of filing. Applicants respectfully submit that the subject matter of the pending claims as amended herewith is adequately supported by the specification and submit that the disclosure provides sufficiently detailed, relevant, and identifying characteristics, both structural and functional, of the claimed

compositions comprising a liposome formulated with an NspA polypeptide as recited. Given the recited structural features of the NspA polypeptide, variants, and fragments, and the recited functional feature that a composition comprising such an NspA polypeptide has the capability to induce an immune response that comprises eliciting antibodies that specifically bind to a polypeptide consisting of the amino acid sequence of SEQ ID NO:2, and given the extensive description in the specification, a person skilled in the art would readily appreciate that at the time of filing Applicants possessed the species encompassed by the claims.

Description that is needed in a specification to support generic claims related to biological subject matter depends on a variety of factors, including "existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (*see Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005)). Thus, the fundamental factual inquiry under the written description requirement focuses on the understanding of *a person skilled in the art*. See also M.P.E.P. § 2163.02.

The present application provides more than a "mere statement" that the claimed polypeptide variants are part of the invention, contrary to the Examiner's assertion, citing case law (*see* Office Action, page 9). In contrast to the present claims, the claims at issue in each of *Fiers v. Ravel* (984 F.2d 1164 (Fed. Cir. 1993)); *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* (927 F.2d 1200 (Fed. Cir. 1991)); and *The Regents of the University of California v. Eli Lilly and Company* (119 F.3d 1559 (Fed. Cir. 1997)), to which the Office Action refers, did *not* recite *any* amino acid or nucleic acid sequence, structure, or formula. Moreover, the Federal Circuit Court of Appeals, confirming that in *Eli Lilly*, the term, "human insulin cDNA," conveyed no relevant structural or physical characteristics, further stated that, "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement" (*see Enzo Biochem* at 964; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003)). Applicants recognize that determining compliance with the written description requirement is a fact-based inquiry that depends on the nature of the invention claimed (*see Enzo Biochem., Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (citing *Vas-Cath*)).

A disclosure naming a single species can support claims to a genus if, as here, the disclosure conveys to a person skilled in the arts the characteristics common to all species. *See In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004). Applicants have described the recited structural features of the NspA polypeptides of the claimed compositions according to common terminology used in the art (*e.g.,* at least 90% identity to the amino acid sequence of SEQ ID NO:2). Contrary to the assertion by the Examiner and as previously made of record, the specification provides guidance, including working examples, that teach a person skilled in the art which particular regions of the NspA polypeptide may be amenable to a substitution, deletion, or addition of an amino acid. The specification describes extensive mutation, modeling, and immunological studies that teach a person skilled in the art which regions of NspA are likely to be immunogenic and which regions are expected to be less immunogenic. As described in the specification and recited in the present claims, immunogenic regions of the Neisseria polypeptide include contiguous amino acids at positions 68-80 and 108-125 of SEQ ID NO:2. Thus, contrary to the assertion by the Examiner, Applicants have described common structural attributes that describe members of the genus of NspA polypeptides recited in the present claims.

The specification thus describes the structural features that correlate with the recited functional characteristic (*i.e.,* capability to elicit antibodies that specifically bind to a polypeptide consisting of SEQ ID NO:2). The specification further describes that exemplary compositions comprising a bacterial phospholipid and an NspA polypeptide when administered to animals induced very high titers of antibodies that bound to NspA and to *N. meningitidis* bacteria, and that had bactericidal activity against different *N. meningitidis* strains (*see, e.g.,* page 57 through page 66 (Examples 9-11; Figures 3 and 4)). In view of the state of the art, given the present description and the high skill level, a person skilled in the art could envision and readily predict that many species would be operable other than those disclosed.

As previously made of record, the basic policy of the Patent Act is to encourage disclosure. *In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976) ("To require disclosures in patent applications to transcend the levels of knowledge of those skilled in the art would stifle the disclosure of inventions in fields man understands imperfectly."). The court in *In re Angstadt* states that "depriving inventors of claims which adequately protect them and limiting them to

claims which *practically invite appropriation of the invention* while avoiding infringement inevitably has the effect of suppressing disclosure." *Id.* at 504 (emphasis added). In particular, if the presently claimed subject matter is limited only to compositions comprising a polypeptide comprising a single, disclosed sequence (*e.g.,* SEQ ID NO:2), a person skilled in the art can readily, and with trivial effort, make polypeptides that are outside the scope of the claim using routine, commonly practiced techniques.

An assertion that the written description requirement is not met unless specific amino acid sequences of each species encompassed by a genus are disclosed grossly underestimates the level of skill and understanding of a person skilled in the microbiology, polypeptide, and immunological arts. Limiting the claims to the amino acid sequence set forth in SEQ ID NO:2 will inevitably invite appropriation of Applicants' inventive efforts related to compositions comprising NspA polypeptides. Moreover, when a person skilled in the art can readily make polypeptides outside the scope of the amino acid sequence of SEQ ID NO:2 that have the recited functions, the person skilled in the art would readily recognize that the application has reasonably conveyed that Applicants possessed the claimed compositions comprising a genus of NspA polypeptides as recited, which are capable of eliciting antibodies that specifically bind to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:2.

The "written description requirement serves a teaching function, a "*quid pro quo*" in which the public is given "*meaningful disclosure* in exchange for being excluded from practicing the invention for a limited period of time." See *University of Rochester v. Searle*, 358 F.3d 916, 922 (Fed. Cir. 2004) (emphasis added), quoting *Enzo*, 323 F.3d at 970. However, requiring Applicants to specifically describe the polypeptide sequence of each embodiment in order to receive claims of sufficient scope to be adequately protective of Applicant's inventive efforts simply does not provide a person skilled in the art with any further "meaningful disclosure" with respect to *practicing* the disclosed and claimed subject matter. Only the *unskilled* artisan, unfamiliar with the instant application and with the tools available in the art to identify NspA variants and immunogenic fragments, requires information on specific amino acid sequences. As noted herein, however, the adequacy of an application's written description is

measured by the understanding of a *person skilled in the art*, and *in haec verba* support is not required (*see, e.g.,* M.P.E.P. § 2163.02). To a *person skilled in the art*, the specification describes immunogenic regions of the NspA polypeptide and describes that this polypeptide elicits an immune response against *N. meningitidis*, which description is sufficiently "meaningful" to practice the full scope of the instant claims, consistent with Applicant's contribution to the immunological and vaccine arts.

Accordingly, Applicants submit that the specification describes the claimed compositions comprising NspA polypeptides, variants and immunogenic fragments thereof, with sufficient, relevant, identifying characteristics to convey to a person skilled in the art that Applicants possessed the claimed embodiments at the time the Application was filed. Thus, all pending claims satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, and Applicants respectfully request withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. § 103

The Examiner rejected claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over Brodeur et al. (WO 96/29412) (Brodeur) in view of any one of Ward et al. (*Microbiol. Pathogenesis* 21:499-512 (1996)) (Ward); Idänpään-Heikkilä et al. (*Vaccine* 13:1501-508 (1995)) (Idänpään-Heikkilä); or Wright et al. (*Infect. Immun.* 70:4028-34 (2002)) (Wright). The Examiner also rejected claims 2-5, 7, 11, 12, 14, 17-21, 23-27, and 34-39 under 35 U.S.C. § 103, alleging that the claimed subject matter is obvious over any one of Cadieux et al. (*Infect. Immun*. 67:4955-59 (1999)) (Cadieux); Plante et al. (*Infect. Immun*. 67:2855-61 (1999)) (Plante); or Martin et al. (*J. Exp. Med.* 185:1173-83 (1997)) (Martin) in view of any one of Ward, Idänpään-Heikkilä, or Wright. The Examiner asserts that each of Brodeur, Cadieux, Plante, and Martin teach a *Neisseria* polypeptide comprising SEQ ID NO:2 and fragments thereof, and that Ward, Idänpään-Heikkilä, and Wright teach incorporation of *N. meningitidis* proteins with liposomes and that a person having ordinary skill in the art would have found it obvious to combine the teachings of any one of Brodeur, Cadieux, Plante, and Martin with Ward, Idänpään-Heikkilä, or Wright to obtain the claimed subject matter.

Applicants traverse these rejections and submit that the Examiner has not established a *prima facie* case of obviousness. The Examiner must, at a minimum, demonstrate that either a single reference or a combination of the cited references teaches or suggests all the features of the claim. If the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason why a person having ordinary skill in the art would combine these features in the fashion claimed by the Applicants with a reasonable expectation of successfully obtaining the claimed subject matter. *See KSR v. Teleflex, Inc.,* 237 S. Ct. 1727, 1741 (2007) ("[A] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art.").

Applicants submit that the cited documents, each alone or in any combination, fail to teach or suggest each feature of the currently pending claims. Neither Brodeur nor any of the other cited documents, Cadieux, Plante, or Martin, teaches or suggests a pharmaceutical composition that combines a liposome comprising a bacterial phospholipid from *N. meningitidis*, *N. lactamica*, or *E. coli* with a NspA polypeptide (*e.g.,* SEQ ID NO:2), variants or fragments thereof. Brodeur lists a liposome, generally, among several forms that a vaccine composition may take and among a list of pharmaceutical adjuvants (*see* Brodeur, page 66). Each of Ward, Idänpään-Heikkilä, and Wright, like Brodeur, fails to teach or suggest a pharmaceutical composition comprising a liposome that comprises a bacterial phospholipid from *N. meningitidis*, *N. lactamica*, or *E. coli* combined with an NspA outer membrane protein.

Viewing the prior art as a whole, the prior art teaches that the immune response induced by a *N. meningitidis* antigen depended upon the combination of the antigen, liposome, and adjuvant. As previously made of record, the teachings of the references fail to indicate that by combining these references, a person having ordinary skill in the art will achieve the claimed embodiments with a reasonable expectation of success. Each of Ward, Idänpään-Heikkilä, and Wright instead suggest that the success was variable and unpredictable when combining the antigen described in each document, respectively, with a liposome to prepare an immunogenic composition.

As discussed in the cited art, despite the similarity in structure of the two outer membrane proteins discussed in each of Ward, Idänpään-Heikkilä, and Wright, different

liposome preparations were required to obtain the desired immune response. Ward determined that the *porA* gene fragment (*i.e.,* class 1 porin; also referred to in the art as class 1 outer membrane protein) was successfully expressed as a recombinant polypeptide only when fused to a bacteriophage coat protein. A composition comprising a phosphatidylcholine-containing liposome and the class 1 outer membrane porin induced bactericidal antibodies when the liposome/porin composition was administered to rabbits in the absence of an additional adjuvant. However, a formulation of the synthetic liposomes with the class 1 outer membrane porin-fusion polypeptide in combination with the adjuvant muramyl dipeptide (MDP) or monophosphoryl lipid A (MPLA) failed to induce bactericidal antibodies (*see* Ward, page 505 "Bactericidal activity of antisera"; Figure 4; discussion, last full paragraph; *see also* Idänpään-Heikkilä). Idänpään-Heikkilä contributes nothing more to the art except to teach that using a different expression system permits expression of the class 1 outer membrane protein without the necessity of fusion to another polypeptide. Idänpään-Heikkilä also formulated the class 1 outer membrane protein with a phosphatidylcholine-containing liposome.

By contrast to the art describing the class 1 outer membrane protein and liposome compositions, addition of the MPLA adjuvant to a phosphatidylcholine-containing liposome composition comprising a different outer membrane protein, the *N. meningitidis* PorB outer membrane protein, significantly enhanced the immunogenicity of PorB. Wright observed that the immune response was enhanced only when MPLA was incorporated into the liposomes with PorB and suggested that MPLA was promoting proper folding of the PorB polypeptide. Even though two *N. meningitidis* outer membrane proteins, Por B and the class 1 outer membrane protein, have highly homologous amino acid sequences and likely form the same three-dimensional structure, and even though these polypeptides were each combined with a common synthetic phospholipid (*i.e.,* phosphotidylcholine), different liposomal formulations were required to obtain the desired immune response (*see* Wright at page 4033, first column; last two paragraphs).

Therefore, from these teachings in the cited art, a person having ordinary skill in the art would not reasonably expect that <u>*any*</u> polypeptide, including a different *N. meningitidis* polypeptide, NspA, described in Brodeur (or in Cadieux, Plante, and Martin) could be combined

with *any* phospholipid to use as an immunogen for inducing an immune response in a host, particularly, for inducing an immune response that comprises bactericidal antibodies. Moreover, totally absent from the teachings or discussion in any of Wright, Ward, or Idänpään-Heikkilä, is any speculation, much less suggestion or teaching, that a person having ordinary skill in the art could successfully obtain Applicants' claimed compositions that comprise a bacterial phospholipid liposome and an NspA polypeptide (or variant or fragment thereof), as recited.

Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants therefore respectfully request that the rejection of the claims be withdrawn.

Applicants submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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MJR:am

Enclosure:
Jódar et al., *Lancet* 359:1499-508 (2002)

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